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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/917,138	07/26/2001	Richard H. Tullis	24730-2207B	4876

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[REDACTED] EXAMINER

SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
1634	[REDACTED]

DATE MAILED: 10/03/2002 

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/917,138	TULLIS ET AL.	
	Examiner Bradley L. Sisson	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) Responsive to communication(s) filed on 11 March 2002.

2a) This action is **FINAL**.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4) Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-18 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1

4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_

5) Notice of Informal Patent Application (PTO-152)

6) Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Location of Application***

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634, and has been assigned to Primary Examiner Bradley L. Sisson.

### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

### **The Quantity of Experimentation Necessary**

The quantity of experimentation need is great, on the order of several man-years and then with little, if any, reasonable expectation of success.

*The Amount of Direction or Guidance Provided and The Presence or Absence of Working Examples*

The specification has been found to provide seven examples:

Example 1, Preparation of DNA Oligonucleotide Probes, pages 14-15;

Example 2, Tailing Reactions Producing Long Polynucleotide Tails, pages 15-17;

Example 3, Labeling and Detection in Solution – Comparison of Hybridization Detection Efficiency of Single Biotin labeled Primer vs. Chain Extended Biotin Primer, page 17;

Example 4, Solid phase Labeling – Determination of Chain Growth Efficiency on Hybridized DNA Probes, page 18;

Example 5, Solid Phase Labeling – Tailing on Probes Bound to Streptavidin-Agarose beads Fluorescein-dUTP and Chain Release with RNase A, pages 18-19;

Example 6, Detection of Chain Growth Directly on Solid Surfaces Using Fluorescein-dUTP Incorporation, page 19; and

Example 7, Detection of Chain Growth Directly on Solid Surfaces Using Biotin-dUTP Incorporation, pages 19-20.

Example 7 is perhaps the most closely related to the method of claims 4-18. As seen at pages 19-20 of the disclosure, the specification teaches that “[t]he plates containing the tailed bound detection probe were washed extensively with 1 x SSC (5 x 300  $\mu$ l at room temperature)

and then treated with 100  $\mu$ l Streptavidin-HRP conjugate (1  $\mu$ g/ml in 1x SSC). After 30 minutes incubation at 37 C, unbound Streptavidin-HRP conjugate was removed by washing several times in 1x SSC."

In contrast to the disclosed method, the claimed method does not require that any washing step be performed at any point in the assay. Consequently, the claimed method encompasses assays where one is attempting to detect a signal where unincorporated and incorporated label are present simultaneously. The specification is silent as to how such can be reproducibly practiced.

#### The Nature of the Invention

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

#### The State of the Prior Art

The state of the art has advanced to the point where certain difficulties are now art-recognized and need to be overcome. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

The specification is essentially silent as to how these art-recognized problems are to be overcome. Applicant's failure to address and overcome these art-recognized problems unfairly shifts the burden of enablement to the public.

*The Relative Skill of Those in the Art*

The relative skill of those in the art that is most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry.

*The Predictability or Unpredictability of the Art*

The predictability of certain problems and difficulties arising is high.

*The Breadth of Scope of the Claims*

The claims have sufficient breadth of scope whereby they encompass the simultaneous assaying of heterogeneous samples under multiplexing conditions. The specification, in comparison, teaches the processing of but one sample that is known and under highly controlled conditions.

complementarity to the target sequence. The publication of Sommer and Tautz teach that primer extension was achieved where but the last three nucleotides of the probe/primer annealed to the target. In such a situation, one would not be able to readily determine if a detectable signal was the product of intended or unintended consequences of probe/primer annealing.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
5. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Steps that will allow or the separation of unused reactants, especially detectable moieties, from the target whereby a useful signal would result.
6. Claims 1-3 are confusing as to what the "method" is for.

### ***Conclusion***

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.
8. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the

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organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

9. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Bradley L. Sisson  
Primary Examiner  
Art Unit 1634

BLS  
September 26, 2002